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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,908	01/29/2007	Yuanchao Li	13369701-0001	3339

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
01/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,908	LI ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7 in the reply filed on 11/24/2008 is acknowledged. The traversal is on the ground(s) that the compounds are novel and therefore the use of the compounds is patentable. This is not found persuasive because reasons of record.

Claims relating to method of using would be subject to rejoinder as indicated in the papers filed 06/23/2008 upon the finding of the allowability of the compound claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-10 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claims. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/24/2008.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 (dependent claims) rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term “linked to C-14” is unclear. What is linked to what is vague.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for few derivatives of triptolide, does not reasonably provide enablement for the wide variety of derivatives encompassed by the formulae. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability

in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

The invention is drawn to derivatives of the natural product triptolide and use of these compounds in the treatment of diseases in which the triptolide has been speculated to be of use.

The claims are drawn to compounds of formulae corresponding to derivatives of triptolide in which the 5, 6 and 14 positions (triptolide numbering) have been modified. These structures vary widely in physical and chemical properties such as stereochemistry, size, molecular weight, logP, acidity, basicity, disposition of variables etc. These factors, known in the art to greatly influence biological properties, because of their wide nature render the breadth of the claims large.

The chemistry direction provided in the specification for **making** the claimed compounds is limited. The enabling chemistry methods for making the claimed derivatives use triptolide as starting materials. The direction, guidance and working example present in the specification all starts with the ability of making 5R, 5-hydroxy compound. The exclusive formation of 5R, and not 5S hydroxy compound in the reaction is indicative of the art recognized limitations in the derivatization of stereochemically complex natural products. It is well known in the art that in the chemistry of structurally complex natural products, that the existing functionalities and

their stereochemical orientation as well as stereochemistry of the ring junctions control the approach of the incoming reagents, thus dictating what the stereochemistry of the newly formed bond would be. Triptolide is a complex natural products with multiple stereocenters and sensitive functionalities such as epoxide functionality. Large majority of the claimed variables are, art recognized to be derivatives of OH group or derivatives susceptible to displacement reactions to make other variables claimed. For example, the inherently present, epoxide functionality is an electrophile, well known in the art to suffer nucleophilic (ring opening) reactions by S and N derived nucleophiles. However, the presence of multiple stereocenters and multiple reactive functionalities in the disclosed starting material severely limit the possibilities for not only the stereochemical possibilities for X and Y, but also the numerous structural possibilities for X and Y. As such, regio- as well as stereo- specific (or at the minimum selective) reactions are required for making the claimed compounds. For example, any attempt to introduce the Y = SR, by either ring opening of 5,6-epoxide, or by displacement of a 6-OH derivative, or by (extended vinylogous) Michael addition to the alpha, beta-unsaturated lactone moiety would be severely compromised by the presence of other multiple functionalities that could compete with such reactions. Likewise, any method of de-oxygenate the 14 positions have to account for the unpredictable participation of several other oxygen functionalities present in the molecule.

The unpredictability of in organic synthesis is high in spite of the high skill level in the area. The state of the art of organic chemical synthesis is closer to what is described by Dorwald et al. who states, “Most non-chemists would probably be horrified

if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface]…….even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]…….. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]…….. As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of

a given starting material, and unexpected products may readily be formed. [8]…….Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, especially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]….." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

What is enabled in the specification is X is alpha OH, X and Y are alpha-OHs (R and S respectively), or together 5,6-alpha-epoxide, 5,6-double-bond. It is not seen where in the specification enabling disclosure with respect to making or using anything other than these possibilities is found. The specification does not disclose alternate methods or prior art citations in lieu of enabling disclosure with respect to how to make these compounds.

Disclosure with respect to potential **'use** aspect' of the enablement requirement is also limited. The disclosed biological data relate to narrowly definable compounds and do not correlate structure with activity. That is, no teaching in the specification is found that would direct and guide one skilled in the art to pick a potentially active compound from the plethora of structures claimed. Further, the wide breadth of the claims defies art recognized concepts relating to, not only organic chemistry methods but also concepts relating to productive small molecule-

macromolecule interaction for biological activity, and finds little support in the specification.

. The quantity of experimentation: For the reasons presented above, there is a substantial gap between what is taught in the specification and what is being claimed. As such, one of ordinary skill in the art would be faced with undue amount of experimentation to identify compound(s) buried in the numerous possibilities encompassed by the formulae. The specification lacks disclosure sufficient to make and use the invention commensurate with the scope of the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation would be required to make and use Applicants' invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claims limited to X and Y as follows would overcome the above rejection:

X = OH (R stereochemistry); Y = OH (S stereochemistry); X and Y together double bond or R,S-epoxide; Z is OH, O, OCOR.

Allowable Subject Matter

Claim 5, 6 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/
Primary Examiner, Art Unit 1625